PhD seminar

"Proline racemase as an innovative target to tackle infectious diseases - Design, synthesis of inhibitors and evaluation of their activity against Trypanosoma cruzi and Clostridioides difficile"

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Proline racemases (PRAC), catalyzing the L-proline and D-proline interconversion, are essential factors in eukaryotic pathogens such as *Trypanosoma cruzi*, a protozoan parasite responsible for Chagas disease, one of the most neglected disease, and *Clostridioides difficile,* an anaerobic Gram-positive bacillus considered as an important nosocomial pathogen that can cause a spectrum of disorders that range in severity from mild diarrhoea to fulminant colitis and/or death. This enzyme, absent in mammals, was first identified and validated in the group of P. Minoprio at Institut Pasteur, Paris, as a new potential therapeutic target against Chagas' disease. As no inhibitor of this target was known, an important multidisciplinary work was conducted, through an innovative modeling strategy of the functional motions of the catalytic pocket of *Tc*PRAC to expand chemical space search in order to identify inhibitors. Hence, two soluble inhibitors of the enzyme were identified by virtual screening on generated models and were validated by radiocrystallography, enzymology and *in vitro* parasite cultures. These compounds were optimized through pharmacomodulations and global optimization of their pharmacologic properties. In continuation to this project, we have taken into account the similarity between *Tc*PRAC and *Cd*PRAC enzymes to design new inhibitors of *Cd*PRAC. This study resulted in promising candidates.